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# Synthesis and Preliminary Biological Evaluation of 4,6-Disubstituted 3-Cyanopyridin-2(1*H*)-ones, a New Class of Calcium Entry Blockers

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**Abstract**—The preparation of 3-cyano-4,6-diaryl-pyridin-2(1H)-ones **4a**–**h**, calcium entry blockers related to diltiazem, is described starting from 1,3-diaryl-2-propen-1-ones **5**. On preliminary pharmacological tests all compounds are active and some of them show calcium antagonistic activity superior or comparable to diltiazem. 

After the introduction of calcium channel blockers (CCBs) into clinical practice,[1] many compounds with calcium antagonistic activity have been described, most of them being structurally related to dihydropyridines (DHPs) nifedipine **1**,[2–5] while very few effective calcium antagonists related to benzothiazepines (BTZs) diltiazem **2** (Fig. 1) have been reported until today. More recently, several novel classes of CCBs have emerged: diphenylbutylpiperidines (fluspirilene),[6,7] 1,3-diphosphonates (belfosdil),[8] and, in addition, benzothiazinone (HOE 166),[9,10] 1,5-benzothiazepines[11] and benzothiazines **3**,[12,13] the chemical structure of which bears some resemblance to diltiazem. In the present paper, we wish to report the synthesis and pharmacological properties of 3-cyano-4,6-diaryl-pyridin-2(1*H*)-ones **4**, a new class of CCBs related to diltiazem.

diltiazem was chosen as the reference compound (template) for a 3D-comparative study in which the structural similarity between this compound and products **4** was investigated. Superimpositions were performed[14] between all the conformers obtained by an extensive conformational analysis executed in a 3.0 kcal/mol energetic window on **4g** (Search/Compare module) and the lowest energy conformation of diltiazem.[13] The moieties to be superimposed were selected taking into account the findings of a previous 3D-QSAR study, in which a hypothesis of the receptor-binding site of diltiazem-like calcium entry blockers was developed.[11] The phenyl ring of diltiazem, which occupies the hydrophobic region 1 of that theoretical model, was superimposed onto the phenolic moiety of **4g** while matching the hydroxyl oxygen with the sulphur atom of diltiazem. Furthermore, the *p*-methoxyphenyl ring of diltiazem was superimposed into the 2,5-dimethoxyphenyl ring of **4g** so that the 5-methoxy group of **4g** could occupy the same position in 3D space occupied by the corresponding functionality of the template. This group was recognised, in fact, to have pharmacophoric relevance, possibly through the interaction with one hydrogen-bonding site of the receptor.[11] The same superimposition procedure could not be applied to nifedipine, due to the lack in this compound of the aromatic ring corresponding to the condensed phenyl of diltiazem.

A very good structural similarity was observed between **4g** and diltiazem. This result is depicted in Figure 1, where the conformer of **4g**, giving the best match, is superimposed onto the template molecule. The distance between the hydrogen at C-5 of the phenolic ring of **4g** and the oxygen at C-4 of the 2,5-dimethoxyphenyl ring of **4g** (both depicted as a ball in Figure 1) was found to

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be 11.7 Å. This value is shorter than the maximum value of 11.8 Å reported as the maximum dimension that CCBs should not exceed to be accepted by their receptor-binding site.[11] A very good match was found between the superimposed aromatic rings as well as an unexpected correspondence in the 3D space between the hydroxyl oxygen of **4g** and the sulphur atom of diltiazem (annotation B in Fig. 1).[15] Finally, proximity in 3D space was observed between the endocyclic nitrogen of diltiazem and the nitrogen atom of **4g**[16a] (annotation A in Fig. 1) and between the ester oxygen of diltiazem and the 2-methoxy oxygen of the dimethoxyphenyl ring of **4g**.[16b]

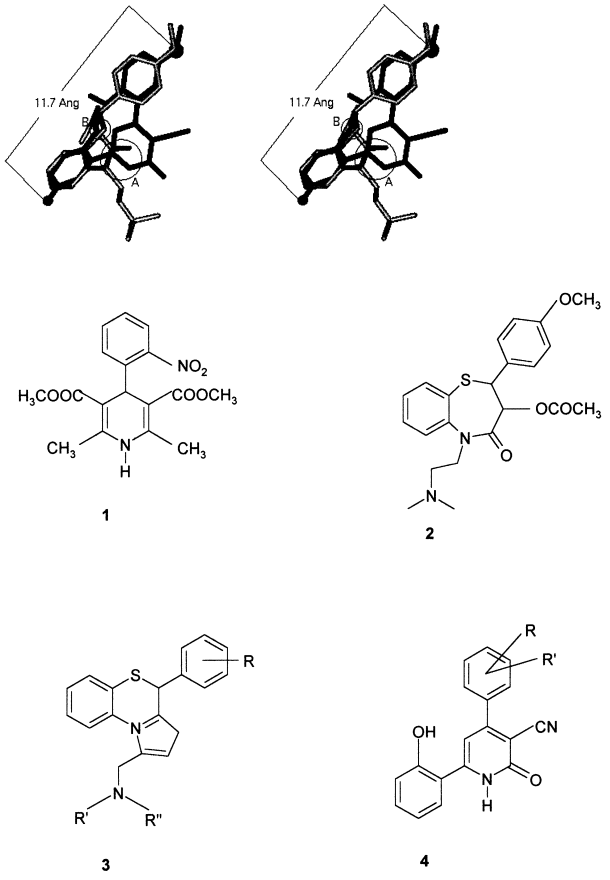



**Figure 1.** Stereo view of the superimposition between **4g** (black) and diltiazem (grey). The sole hydrogen at C-5 of the phenolic ring of **4g** is displayed (smaller ball). Annotation A highlights the proximity between the endocyclic nitrogen of diltiazem and the nitrogen atom of **4g**. Annotation B highlights the correspondence in 3D space between the hydroxyl oxygen of **4g** and the sulphur atom of diltiazem.

Therefore, we synthesised the family of compounds **4a**–**h** in order to assess their antagonistic properties. The 3-cyano-4-(*R*,*R*′-aryl)-6-(2-hydroxyphenyl)-2(1*H*)-pyridones were prepared as previously reported,[17] by reaction of substituted 1,3-diaryl-2-propen-1-ones **5** with ethyl cyanoacetate in the presence of ammonium acetate. Substituted 1,3-diaryl-2-propen-1-ones were obtained by condensation of *o*-hydroxyacetophenone **6** with substituted benzaldehydes **7** (Scheme 1) (Table 1).

## Pharmacology

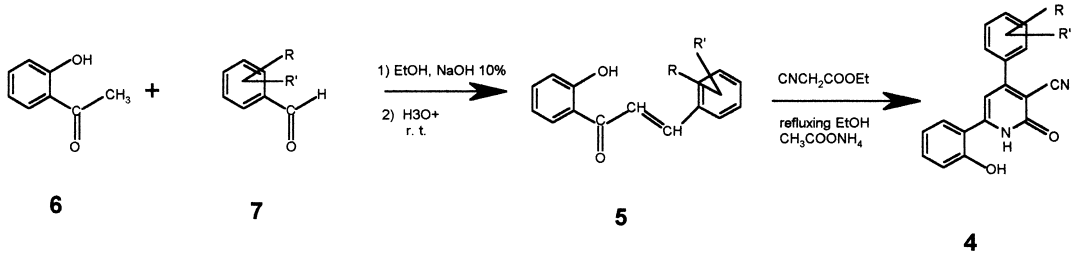
Compounds **4a**–**h** were tested in vitro on $K^+$-depolarised rat aorta strips[18] to evaluate their ability to relax the initial contraction induced by $K^+$ ($IC_{50}$ values) and activity in maximum smooth muscle relaxation (maximum relaxation %). Pharmacological data are reported in Table 2. All compounds examined displayed a good vasorelaxing activity and, while **4c**,**f**,**h** were less active, **4a**,**b**,**d**,**e**,**g** were from 2- to 10-fold more potent than diltiazem in $IC_{50}$ assay and showed also a good maximum smooth muscle relaxing ability. These results confirmed the molecular modelling predictions regarding the interaction of 2(1*H*)-pyridone derivatives with the active site of L-type calcium channels[20] and showed that there are possible other modifications of the structure of diltiazem with retention of the inhibitory activity.

In conclusion, we synthesised some 3-cyano-4-(*R*,*R*′α-aryl)-6-(2-hydroxyphenyl)-2(1*H*)-pyridones **4a**–**h** which could be considered a novel class of CCBs related to diltiazem, characterised by the contraction of the seven-membered ring together with elimination of the condensed benzene nucleus. Some of them showed potent calcium blocking properties in pharmacological tests.

**Table 1.** Chemical and physical data (**4a**–**h**)

| Compound | *R* | *R*′ | Yield (%) | Mp (°C) | Formula[a] |
|---|---|---|---|---|---|
| **4a** | H | H | 40 | 280–281 | $C_{18}H_{12}N_2O_2$ |
| **4b** | H | 2-Cl | 30 | 210–212 | $C_{18}H_{11}N_2O_2Cl$ |
| **4c** | H | 2-Br | 30 | 309–310 | $C_{18}H_{11}N_2O_2Br$ |
| **4d** | H | 2-$CH_3$ | 20 | 265–266 | $C_{19}H_{14}N_2O_2$ |
| **4e** | H | 2-$OCH_3$ | 27 | 318–320 | $C_{19}H_{14}N_2O_3$ |
| **4f** | 2-$OCH_3$ | 4-$OCH_3$ | 25 | Oil | $C_{20}H_{16}N_2O_4$ |
| **4g** | 2-$OCH_3$ | 5-$OCH_3$ | 20 | 255–258 | $C_{20}H_{16}N_2O_4$ |
| **4h** | H | 3-$NO_2$ | 55 | 332–333 | $C_{18}H_{11}N_3O_4$ |

[a]Results of elemental analysis were ±0.4% of theoretical values; NMR and IR spectra confirmed the assigned structures.




**Scheme 1.**

**Table 2.** Inhibiting and vasorelaxing activity (**4a–h**)

| Compound | $IC_{50}$ (M) | Maximum relaxation concn (M) | Maximum relaxation (%) |
|---|---|---|---|
| diltiazem | $4.8\times10^{-8}$ | $10^{-4}$ | 97.86 |
| **4a** | $9.5\times10^{-10}$ | $10^{-4}$ | 23.86 |
| **4b** | $3.0\times10^{-8}$ | $10^{-4}$ | 79.78 |
| **4c** | $1.7\times10^{-5}$ | $10^{-4}$ | 35.29 |
| **4d** | $1.0\times10^{-6}$ | $10^{-4}$ | 89.17 |
| **4e** | $1.2\times10^{-8}$ | $10^{-4}$ | 99.54 |
| **4f** | $3.8\times10^{-7}$ | $10^{-4}$ | 40.00 |
| **4g** | $1.1\times10^{-9}$ | $10^{-5}$ | 95.51 |
| **4h** | $5.0\times10^{-7}$ | $10^{-4}$ | 64.00 |

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16. The two atoms were 1.36 Å from each other. (b) The two atoms were 1.19 Å from each other.
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